(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 695 545 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
07.02.1996 Bulletin 1996/06

(21) Application number: **95109239.4**

(22) Date of filing: **14.06.1995**

(51) Int. Cl.[6]: **A61K 31/135**, A61K 31/22, A61K 31/395, A61K 31/445

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **06.07.1994 JP 154504/94**

(71) Applicant: **Mitsubishi Chemical Corporation**
Chiyoda-ku Tokyo (JP)

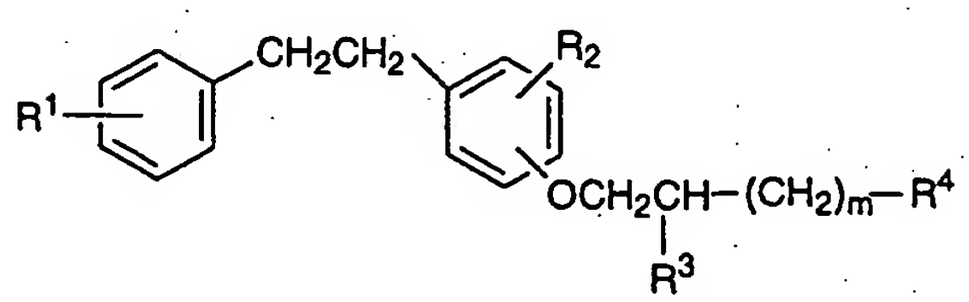
(72) Inventor: **Mano, Tomiya**
Ibaraki-shi, Osaka-fu (JP)

(74) Representative: **Hansen, Bernd, Dr. Dipl.-Chem. et al**
D-81925 München (DE)

(54) Use of diphenylethane derivatives for the treatment of glaucoma

(57) The present invention provides a novel drug for treating glaucoma.

The present invention relates to a therapeutic agent for glaucoma and an ocular hypotensive agent, which comprise an aminoalkoxybibenzyl represented by the formula (I):



... (I)

wherein R^1 represents a hydrogen atom, a C_1-C_5 alkoxy group, etc.; R^2 represents a hydrogen atom, a halogen atom, etc.; R^3 represents a hydrogen atom, a hydroxyl group, -O-CO-$(CH_2)_l$-COOH (wherein l is an integer of 1 to 3), etc.; and R^4 represents -NR^5R^6 (wherein R^5 and R^6 independently represent a hydrogen atom or a C_1-C_8 alkyl group), etc. or a salt thereof as an active ingredient.

EP 0 695 545 A1

Printed by Rank Xerox (UK) Business Services
2.9.9/3.4

Description

FIELD OF THE INVENTION

The present invention relates to a therapeutic agent for ophthalmic disease comprising aminoalkoxybibenzyls or a salt thereof as an active ingredient. More particularly, it relates to a therapeutic agent for glaucoma, and an ocular hypotensive agent.

BACKGROUND OF THE INVENTION

Glaucoma is considered to be a group of diseases wherein the entoptic tissue (particularly function of optic nerve cell) is damaged from lesions causing an abnormal ocular tension. Normally, the principal factors of the mechanism causing lesions are considered to be ischemic symptoms and disorder of optic nerve axonal flow due to mechanical compression in the lamina cribrosa caused by an increase in ocular tension. However, the mechanism of the increase in ocular tension is not clear at present. Further, in Japanese Patent Publication No. 13427/1988, the structure of aminoalkoxybibenzyls and a salt thereof is described. It is also described that they has an effect to increase an anticoagulant action and a prostaglandin I_2 action.

The significance of glaucoma as degenerative diseases has been increasing in advanced nations which have already entered in an ultra aging society, and good remedies for glaucoma have been requested still now.

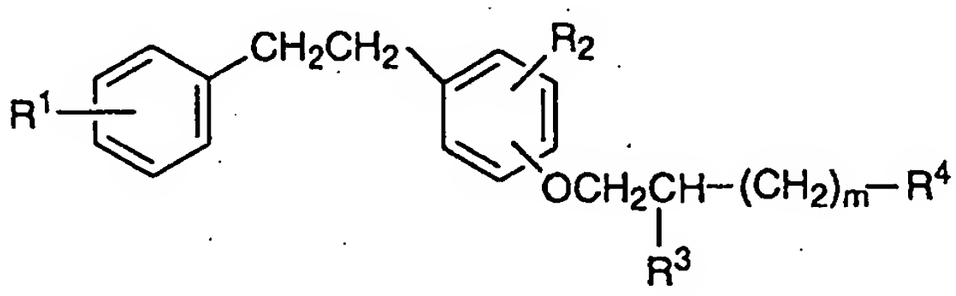
SUMMARY OF THE INVENTION

In order to solve the above problems, the present inventors have studied intensively. As a result, it has been found that aminoalkoxybibenzyls having a specific structure or a salt thereof has an ocular tension reducing action and is useful for treating glaucoma, and the present invention has been accomplished.

The main object of the present invention is to provide a therapeutic agent for glaucoma and an ocular hypotensive agent.

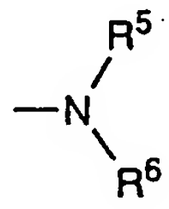
This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description.

The present invention provides a therapeutic agent for glaucoma and an ocular hypotensive agent, which comprise an aminoalkoxybibenzyl represented by the general formula (I):



... (I)

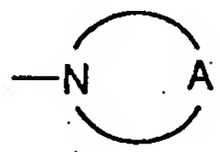
wherein R^1 represents a hydrogen atom, a halogen atom, a C_1-C_5 alkoxy group or a C_2-C_8 dialkylamino group;
R^2 represents a hydrogen atom, a halogen atom or a C_1-C_5 alkoxy group;
R^3 represents a hydrogen atom, a hydroxyl group, $-O-(CH_2)_n-COOH$ (wherein n is an integer of 1 to 5) or $-O-CO-(CH_2)_l-COOH$ (wherein l is an integer of 1 to 3);
R^4 represents a group of the general formula:



wherein R^5 and R^6 independently represent a hydrogen atom or a C_1-C_8 alkyl group,

or

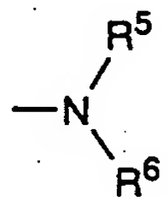
a group of the general formula:



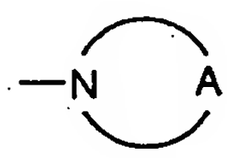
wherein A is a C_3-C_5 alkylene group which may be substituted with a carboxyl group;
and
m is an integer of 0 to 5,
or a salt thereof as an active ingredient.

DETAILED DESCRIPTION OF THE INVENTION

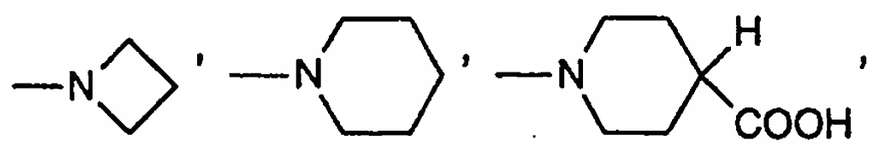
The definition in the above formula will be explained in detail hereinafter. R^1 represents a hydrogen atom, a halogen atom (e.g. a chlorine atom, a fluorine atom, etc.), a C_1-C_5 alkoxy group (e.g. a methoxy group, an ethoxy group, a butoxy group, etc.) or a C_2-C_6 dialkylamino group (e.g. a dimethylamino group, a diethylamino group, a methylethylamino group, etc.); R^2 is a hydrogen atom, a halogen atom (e.g. a chlorine atom, a fluorine atom, etc.) or a C_1-C_5 alkoxy group (e.g. a methoxy group, an ethoxy group, a butoxy group, etc.);
R^3 represents a hydrogen atom, a hydroxyl group, -O-$(CH_2)_n$-COOH (wherein n is an integer of 1 to 5) such as -O-$(CH_2)_2$-COOH, -O-$(CH_2)_3$-COOH, etc. or -O-CO-$(CH_2)_l$-COOH (wherein l is an integer of 1 to 3) such as -O-CO-$(CH_2)_2$-COOH, -O-CO-$(CH_2)_3$-COOH, etc.;
R^4 represents a group of the general formula:



wherein R^5 and R^6 independently represent a hydrogen atom or a C_1-C_8 alkyl group such as a methyl group, a butyl group, hexyl group, a heptyl group, etc., such as an amino group, a methylamino group, an ethylamino group, a butylamino group, a hexylamino group, a heptylamino group, a dimethylamino group, a diethylamino group, a methylethylamino group, etc.,
or
a group of the general formula:

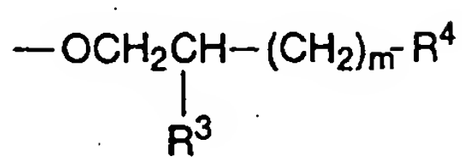


wherein A represents a C_3-C_5 alkylene group which may be substituted with a carboxyl group, such as

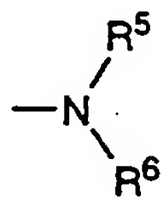


etc.;
and
m is an integer of 0 to 5.

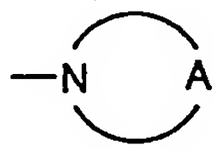
In the present invention, the aminoalkoxy group of the formula:



is preferably positioned on the 2-position in the aminoalkoxybibenzyl of the formula (I). Further, R^1 is preferably a hydrogen atom, a C_1-C_5 alkoxy group or a C_2-C_6 dialkylamino group. R^2 is preferably a hydrogen atom. R^4 is preferably a group of the formula:



wherein at least one of R^5 and R^6 is a C_1-C_8 alkyl group, or
a group of the formula:

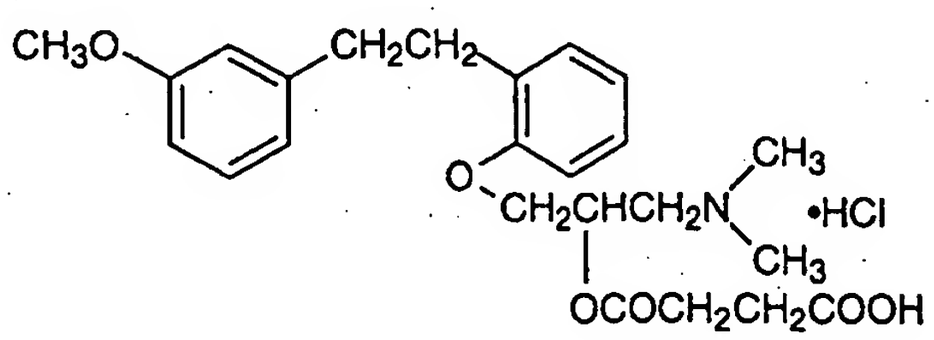


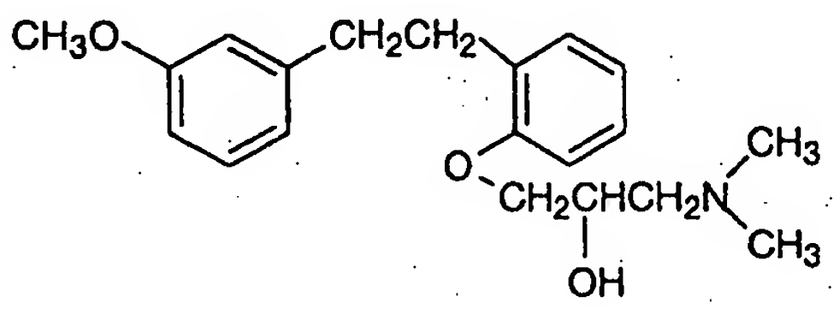
wherein A is a methylene group.
m is preferably an integer of 0 to 2.

Further, pharmaceutically acceptable acid addition salts of the above compounds may also be included in the scope of the present invention.

Examples of the acid addition salt include addition salts of acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, acetic acid, succinic acid, adipic acid, propionic acid, tartaric acid, maleic acid, oxalic acid, citric acid, benzoic acid, toluenesulfonic acid, methanesulfonic acid and the like.

Among aminoalkoxybibenzyls to be used in the present invention, examples of the most preferred compound include the following compounds:





or its salts.

The above aminoalkoxybibenzyls to be used in the present invention are known compounds and can be easily synthesized, for example, by the method described in Japanese Patent Publication No. 13427/1988.

The therapeutic agents of the present invention may be oral agents, injections, eye drops, ointments and the like. For oral agents, they may be tablets, capsules, powders, liquid preparations, elixirs and the like. Non-toxic solids or liquids can be contained in the therapeutic agent as a pharmaceutically acceptable carrier.

When the solid carrier is used, there is exemplified a conventional gelatin-type capsule. Further, an active ingredient can be used with or without auxiliaries to form a tablet or a powder packing.

These capsules, tablets and powders contain normally 5 to 95 % by weight, preferably 25 to 90 % by weight, of the active ingredient.

That is, these dosage forms can contain 5 to 500 mg, preferably 25 to 250 mg, of the active ingredient per dose.

As the liquid carrier, there can be used water, oils originated from animals/vegetables (e.g. petroleum, peanut oil, soybean oil, mineral oil, sesame oil, etc.) or synthetic oils.

As the liquid carrier, there can be suitably used saline, dextrose or similar sucrose solution, glycols (e.g. propylene glycol, polyethylene glycol, etc.) and the like. Particularly, an injection using saline contains normally 0.5 to 20 % by weight, preferably 1 to 10 % by weight, of the active ingredient.

In case of the liquid preparation for oral administration, a suspension or syrup containing 0.5 to 10% by weight of the active ingredient is preferred. In this case, aqueous excipients (e.g. flavor, syrup, pharmaceutical micelle, etc.) may be used as the carrier.

In order to prepare the eye drop, various additives described below may be appropriately added to a solution obtained by dissolving aminoalkoxybibenzyls represented by the formula (I) in water.

As a buffer, for example, there can be used phosphate buffer, borate buffer, tartrate buffer, acetate buffer, amino acid and the like.

As an isotonicity, for example, there can be used sugars (e.g. sorbitol, glucose, mannitol, etc.), polyhydric alcohols (e.g. glycerine, propylene glycol, etc.), salts (e.g. sodium chloride, etc.) and the like.

As an antiseptic, for example, there can be used quaternary ammonium salts (e.g. benzalkonium chloride, benzethonium chloride, etc.), paraoxybenzoates (e.g. methyl paraoxybenzoate, ethyl paraoxybenzoate, etc.), benzyl alcohol, phenethyl alcohol, sorbic acid and a salt thereof, thimerosal, chlorobutanol and the like.

As a viscous agent, for example, there can be used hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose and a salt thereof.

An ointment can be prepared by homogeneously mixing an aminoalkoxybibenzyl of the general formula (I) with a suitable base (e.g. vaseline, etc.) and optionally adding preservatives, stabilizers or other suitable additives.

The dose of aminoalkoxybenzyls of the formula (I) contained in the preparations of the present invention varies depending upon the patient's age, weight and symptoms, severity of diseases and the like, and it should be finally decided by the clinical doctor. It is administered with a daily dose of normally 0.5 to 50 mg/kg, preferably 1 to 30 mg/kg, for one or more days. When the preparation of the present invention is the oral agent, 50 mg or 100 mg of the aminoalkoxybibenzyl are contained in the unit dosage form. For example, it is normally administered 1 to 3 times per day with a dose

of 100 mg/time. In the case of the injection, the aminoalkoxybibenzyl is normally administered 1 to 4 times per day with a dose of 10 to 30 mg/time. In the case of the eye drop, an eye drop containing the amonoalkoxybibenzyl in a concentration of 0.1 to 1 % is prepared and the eye drop is administered 1 to 4 times per day.

The preparations of the present invention can be widely applied in the ophthalmic field on the basis of an ocular hypotensive action of the aminoalkoxybibenzyls. For example, the preparations containing the aminoalkoxybibenzyls as the active ingredient of the present invention are useful for preventing or treating glaucoma, ocular hypertension and the like. Further, glaucoma include high tension glaucoma and low tension glaucoma (normal tension glaucoma) wherein glaucomatous abnormalities of optic disk and glaucomatous abnormalities of the visual field are recognized while exhibiting normal ocular tension. The preparations of the present invention are effective for the both and is particularly effective for high tension glaucoma.

The following Examples further illustrate the present invention in detail but are not to be construed to limit the scope thereof.

Example 1

To patients having an ocular tension of more than 21 mmHg, a preparation containing 100 mg of salpoglelate hydrochloride (chemical name: (±)-1-[o-[2-(m-methoxyphenyl)ethyl]phenoxy]-3-(dimethylamino)-2-propyl hydrogensuccinate hydrochloride) was administered orally 3 times per day for 1 to 3 weeks to examine oral hypotensive action for the salpoglelate hydrochloride.

The results are shown in Table 1, below. In Table 1, the value of ocular tension immediately before administration of this preparation, the value after administration for a predetermined period and the value after a predetermined period has passed since the completion of the administration of this preparation are shown in the items of "before administra-

tion", "during administration" and "after completion of administration", respectively.

Table 1

No.	Initial	Sex	Age		Ocular tension (mmHg)			
					Before administration	During administration	After completion of administration	
1	S.H.	F	70	Date	3/1	3/8	3/18	3/25
				Right	26	21	21	22
				Left	23	21	19	19
2	N.N.	M	68	Date	2/15	2/22	3/22	4/5
				Right	26	18	21	17
				Left	18	16	15	15
3	T.K.	M	50	Date	2/18	2/22	3/22	
				Right	20	15	20	
				Left	18	14	18	
4	D.T.	M	54	Date	2/14	2/28	3/28	
				Right	28	22	33	
				Left	27	22	25	
5	R.A.	F	23	Date	2/15	3/1	4/5	
				Right	28	24	23	
				Left	26	23	25	
6	K.N.	F	48	Date	2/22	3/1	3/11	3/25
				Right	30	23	27	27
				Left	30	22	25	24
7	T.M.	M	51	Date	2/22	3/1	4/5	
				Right	23	19	18	
				Left	23	18	17	
8	K.M.	F	58	Date	2/22	3/1	4/5	
				Right	25	22	24	
				Left	23	22	21	

9	Y.M.	F	72	Date	2/22	3/1	3/22		
				Right	22	24	18		
				Left	16	18	19		
10	S.T.	F	68	Date	2/4	2/18	3/4	3/18	4/1
				Right	28	25	26	28	27
				Left	25	25	26	27	25
11	K.T.	F	65	Date	2/22	3/1		3/15	4/5
				Right	26	22		26	28
				Left	26	22		22	28
12	M.N.	F	65	Date	2/4	2/15	3/4		
				Right	24	17	21		
				Left	20	18	17		
13	K.K.	F	25	Date	2/22	3/1		3/22	
				Right	25	20		21	
				Left	15	13		14	
14	H.N.	M	69	Date	2/25	3/4		4/1	
				Right	23	22		24	
				Left	21	19		22	
15	T.I.	M	63	Date	3/1	3/8		3/15	3/29
				Right	26	19		19	16
				Left	26	19		19	16
16	T.S.	F	62	Date	3/1	3/8		3/15	3/29
				Right	24	21		21	20
				Left	26	23		23	20
17	E.K.	M	61	Date	2/18	2/25			
				Right	18	16			
				Left	28	23			
18	K.T.	F	45	Date	3/25	4/1			
				Right	26	23			
				Left	26	23			

19	T.S.	M	64	Date	3/10	3/17		
				Right	21	21		
				Left	16	13		
20	R.O.	M	78	Date	2/22	3/1	3/7	3/22
				Right	28	28	28	25
				Left	22	22	22	22
21	Z.I.	M	59	Date	2/18	3/1	3/8	3/29
				Right	38	16	16	13
				Left	29	19	18	14
22	K.A.	M	50	Date	2/9	2/15		
				Right	17	17		
				Left	29	44		
23	M.E.	M	64	Date	2/15	2/16	2/25	3/4	3/11
				Right	17	17	16	19	20
				Left	23	35	21	19	20
24	T.N.	M	55	Date	3/15	3/22		
				Right	21	19		
				Left	21	19		
25	T.T.	M	70	Date	3/15	3/22	4/5	
				Right	24	17	16	
				Left	21	17	17	
26	M.I.	F	57	Date	3/15	3/22	4/5	
				Right	33	27	27	
				Left	32	27	26	
27	H.I.	M	56	Date	3/1	3/5	3/8	4/5
				Right	21	23	19	21
				Left	29	30	22	20
28	T.T.	M	63	Date	3/11	3/14	3/18	3/25
				Right	40	29	29	15
				Left	19	17	16	14

Ocular tension was not changed in five cases (10, 14, 20, 23 and 24) and the ocular tension of the case 22 was increased. However, the ocular tension was decreased by 3 mm Hg or more in other cases. It can be judged from these

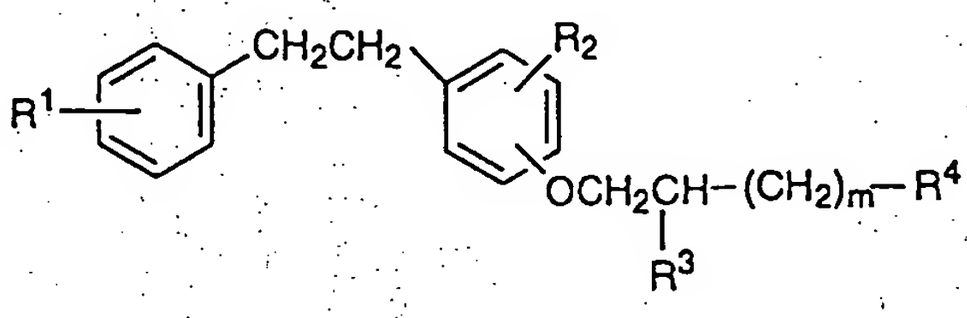
data that salpoglelate hydrochloride has the ocular hypotensive action. Further, the above data shows that the ocular hypotensive is maintained even if the administration of salpoglelate chloride is stopped. Accordingly, salpoglelate hydrochloride is useful as the ocular hypotensive agent.

Furthermore, it is a good therapeutic means for glaucoma to decrease the ocular tension so that salpoglelate hydrochloride is considered to be useful as a therapeutic agent for glaucoma, particularly glaucoma accompanied with a increase in ocular tension.

Further, particularly significant side effects were not recognized in all cases.

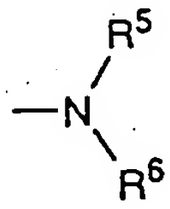
Claims

1. Use of aminoalkoxybibenzyl compounds represented by formula (I) and/or their pharmaceutically acceptable salts for the manufacture of an ocular hypotensive agent or a medicament for the treatment of glaucoma:

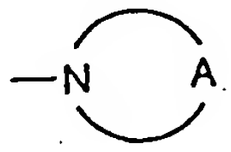


... (I)

wherein R^1 represents a hydrogen atom, a halogen atom, a C_1-C_5 alkoxy group or a C_2-C_8 dialkylamino group;
R^2 represents a hydrogen atom, a halogen atom or a C_1-C_5 alkoxy group;
R^3 represents a hydrogen atom, a hydroxyl group, -O-$(CH_2)_n$-COOH (wherein n is an integer of 1 to 5) or -O-CO-$(CH_2)_l$-COOH (wherein l is an integer of 1 to 3);
R^4 represents a group of the general formula:

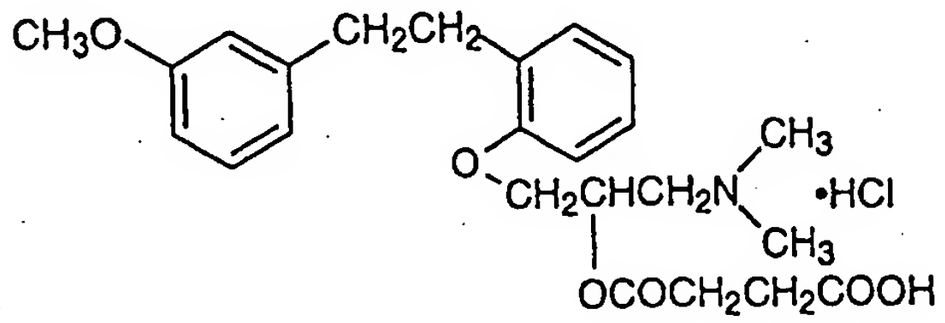


wherein R^5 and R^6 independently represent a hydrogen atom or a C_1-C_8 alkyl group,
or
a group of the general formula:

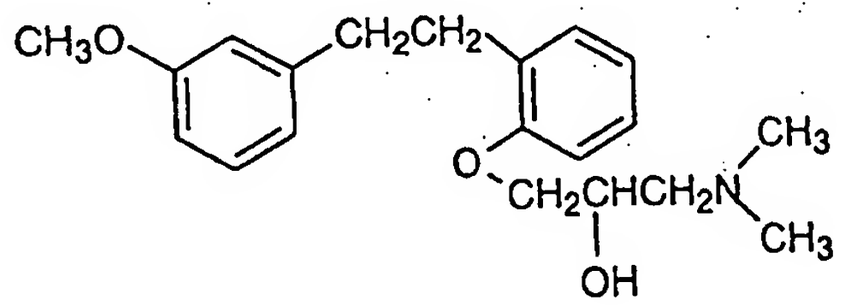


wherein A represents a C_3-C_5 alkylene group which may be substituted with a carboxyl group;
and m is an integer of 0 to 5.

2. Use according to claim 1 whereby the compound represented by formula (I) is:



3. Use according to claim 1 whereby the compound represented by formula (I) is:



4. Use according to claims 1 to 3 for the manufacture of oral administration forms.

5. Use according to claims 1 to 3 for the manufacture of injection solutions.

6. Use according to claims 1 to 3 for the manufacture of eye drops.

7. Use according to claims 1 to 3 for the manufacture of ointments.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 10 9239

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
P,X	DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US Acc. No. 11649054. , 1995 H. TAKENAKA ET AL 'The effect of Anplag (Sarpogrelate HCl), novel selective 5-HT2 antagonist on intraocular pressure in glaucoma patients. ' * abstract * & INVEST. OPHTHALMOL VISUAL SCI., vol. 36, no. 4, 1995 page s734 ---	1-7	A61K31/135 A61K31/22 A61K31/395 A61K31/445
D,A	EP-A-0 072 942 (MITSUBISHI CHEMICAL INDUSTRIES LTD.) 2 March 1983 -----		

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	30 October 1995	Klaver, T

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)